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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
DEBERRY, REGINA M

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 06/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/893,339	ROSENTHAL ET AL.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-52* is/are pending in the application.

4a) Of the above claim(s) *20-23,25,26,35 and 37-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19,24,27-34,36,47 and 49-52* is/are rejected.

7)☒ Claim(s) *48* is/are objected to.

8)☒ Claim(s) *1-52* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Status of Application, Amendments and/or Claims

The information disclosure statement filed 20 May 2002 (Paper No. 5) was received and complies with the provisions of 37 CFR §§1.97 and 1.98. It has been placed in the application file and the information referred to therein has been considered as to the merits.

Applicant's species election of G-CSF and hydroxypropyl methylcellulose in Paper No. 7 (22 October 2002) is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Applicant's species election of polyoxypropylene in Paper No. 10 (24 February 2003) is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 20-23, 25, 26, 35, 37-46 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Claims 1-19, 24, 27-34, 36, 47-52 are under examination.

Election was made **without** traverse in Paper No. 7 and 11.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 29 and 31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 29 is indefinite because it contains an improper Markush group.

Claim 31 recites the limitation "wherein the pycocolloid comprises agar". There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4-13, 15-19, 24, 27-34, 36, 49-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stratton *et al.* (US Patent 5,861,174, reference submitted by Applicant, IDS#3) in view of Gentz *et al.*, US Patent No. 6,238,888 B1.

Stratton *et al.* (US Patent 5,861,174, reference submitted by Applicant, IDS#3) teach pharmaceutical compositions for delivery of pharmacologically active proteins comprising polyoxyethylene-polyoxypropylene (first biocompatible polymer) to humans or animals (abstract and column 3, lines 64-67). Polyoxyethylene-polyoxypropylene may

be represented by the formula HO(C2H4))b(C3H6O)a(C2H4O)bH wherein a and b are integers such that the hydrophobe base represented by (C3H6)a has a molecular weight ranging from about 900 to 4,000, as determined by hydroxyl number and the polyoxyethylene chain consisting of at least 60 to 70% by weight of the copolymer (abstract; column 2, lines 18-50 and column 4, line 63-column 5, line 19). Stratton *et al.* teach specific examples of polypeptides suitable for incorporation in the delivery system include colony-stimulating factors (column 5, lines 51-56) (claims 1, 8-17). Stratton *et al.* teach a pharmaceutical composition wherein combined protein forms a homogenous suspension of fine particles in the polymer solution. Raising the sample temperature above the gel point of the polaxamer results in an even distribution of protein particles throughout the polymer gel. The liquid to gel transition is fully reversible upon cooling. The composition can be implanted directly into the body by injecting it as a liquid which will gel once inside the body (column 5, line 61-column 6, line 20) (claims 34, 49-52). Stratton *et al.* do not teach a second biocompatible polymer, the molecular weight range of a second biocompatible polymer, viscosity or the first and second temperature.

Gentz *et al.*, US Patent No. 6,238,888 B1, teach a pharmaceutical formulation comprising keratinocyte growth factor-2 polypeptide, a buffer and polyoxyethylene-polyoxypropylene block copolymer (first biocompatible polymer) and hydroxypropylmethyl cellulose (HPMC)(second biocompatible polymer) (column 2, lines 37-51) (claim 1). Thickening agents (HPMC) increase the viscosity of the formulation and should raise the viscosity to about 50 to about 10,0000 cps (column 7, lines 50-64 and column 8, lines 14-15) (claim 5). The cellulose derivative (HPMC) has a molecular

weight in the range of about 80,000 to about 240,000 (column 8, lines 11-16) (claims 17, 33). Thickening agents may added to the injectable formulations (column 8, lines 17-18) (claim 49). Polyoxyethylene-polyoxypropylene block copolymers exhibit reverse thermal gelation behavior. The gel is a low viscosity aqueous solution at room temperature, but when it contacts the mammalian body and is warmed by body temperature the viscosity increases as the solutions gels (column 9, lines 52-67) (claims 4, 6). Gentz *et al.* teach the use of the pharmaceutical composition in mammals including humans (column 22, lines 48-52) (claims 51, 52).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Stratton *et al.* and Gentz *et al.* to make the instant composition. The motivation and expected success is provided by both Stratton and Gentz. Stratton *et al.* teach the use of polyoxyethylene-polyoxypropylene block copolymers for sustained release delivery systems. Polyoxyethylene-polyoxypropylene block copolymers exhibit reverse thermal gelation behavior. Gentz *et al.* teach the use of HPMC to increase the viscosity of the pharmaceutical compositions.

Claims 27-32, 36 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stratton *et al.* (US Patent 5,861,174, reference submitted by Applicant, IDS#3) and Gentz *et al.*, US Patent No. 6,238,888 B1 as applied to claims 1, 4-13, 15-19, 24, 27-34, 36, 49-52 and in further view of Roos *et al.*, US Patent No. 5,840,338.

The teachings of Stratton *et al.* and Gentz *et al.* are described above. None of the references teach a second biocompatible polymer comprising a second biocompatible polymer, granulocyte stimulating factor (G-CSF) or an antigen.

Roos *et al.*, US Patent No. 5,840,338 teach that biologically active solutes such as proteins can be loaded into safe, responsive crosslinked polysaccharide gel networks and demonstrate activity after exposure to thermal and chemical challenges. Roos *et al.* teach the effects of crosslinked polysaccharide gel networks such as hydroxypropyl cellulose (second biocompatible polymer) crosslinked with adipic acid using loading solutions containing PLURONIC. PLURONIC polymers are polyoxyalkylene derivatives of propylene glycol (difunctional block polymers) (first biocompatible polymer) (column 3, lines 9-13 and 31-45) (claim 7). Roos *et al.* teach a drug delivery system comprising a polymer gel network including the drug to be delivered, a salt and a loading polymer (column 4, lines 35-43). Hydroxypropylmethycellulose (HPMC) and modified food starch are preferred polysaccharide (column 6, lines 30-44). Exemplary cellulose ethers include HPMC (column 41, lines 18-28) (claims 18 and 19). Biologically active solutes include any material that is soluble, may in principle, be loaded with the present method. The solutes are biologically active solutes that are susceptible to being denatured or otherwise inactivated and that have biological and/or chemical activity when active (column 21, lines 7-12). Examples of active biologically active solutes include oral hepatitis B vaccine (column 8, lines 21-35) and granulocyte colony stimulating factor

(column 25, line 11) (claims 36, 47). Polymeric starting materials including agar, alginate, carrageenan and starch (column 41, lines 5-17)(claims 27-32).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Stratton *et al.*, Gentz *et al.* and Roos *et al.* to make the instant composition. The motivation and expected success is provided by Roos *et al.* Roos *et al.* teach that granulocyte colony stimulating factor can be loaded into a polysaccharide gel networks drug delivery system (comprising HPMC and polyoxyethylene-polyoxypropylene), demonstrate activity after exposure to thermal and chemical challenges and is safe for use in humans.

Claims 2 and 3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stratton *et al.* (US Patent 5,861,174, reference submitted by Applicant, Paper No. 5) and Gentz *et al.*, US Patent No. 6,238,888 B1 as applied to claims 1, 4-13, 15-19, 24, 27-34, 36, 49-52 and in further view of Chan *et al.* (US Patent No. 5,702,717, reference submitted by Applicant, Paper No. 5).

The teachings of Stratton *et al.* and Gentz *et al.* are described above. None of the references teach a first temperature lower than 20C or within a range from 1C to 20C and the second temperature higher than 25C.

Chan *et al.* teach that the triblock of poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) are marketed under the Pluronic tradenames (column 3, lines 36-46). The triblock copolymers undergo solidification or gelation as the temperature of the

solution is raised above a critical temperature. The polymers form micelles at low concentration and turn into thick, continuous gels at high concentrations and elevated temperatures (column 3, lines 51-56). Chan *et al.* teach the gel properties of Pluronic-6, Pluronic F-68, Pluronic F-88 and Pluronic F-108. Pluronic F-88 forms a gel at 40% at 25C, Pluronic F-127 forms a gel at 20% concentration at 20C (column 3, line 58-column 4, line 39 and Table 1).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Stratton *et al.*, Gentz *et al.* and Chan *et al.* to make the instant composition. The motivation and expected success is provided by Stratton, Gentz and Chan. Stratton *et al.* teach the use of polyoxyethylene-polyoxypropylene block copolymers for sustained release delivery systems. Polyoxyethylene-polyoxypropylene block copolymers exhibit reverse thermal gelation behavior. Gentz *et al.* teach the use of HPMC to increase the viscosity of the pharmaceutical compositions. Chan *et al.* teach the physicochemical characteristics and gel forming properties of various polyoxyethylene-polyoxypropylene block copolymers. The gelation temperature ranges taught by Chen *et al.* provide reverse-thermal viscosity at temperatures below the physiologic temperature of the host.

Claim Objections

Claim 48 is object to for depending from a rejected claim.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (703) 305-6915. The examiner can normally be reached on 9:00 a.m.-6:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

RMD
May 21, 2003

ELIZABETH KEMMERER
PRIMARY EXAMINER